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NIH Fiche to Paper Journal

TITLE:	CLINICAL ENDOCRINOLOGY
PUBLISHER/PLACE:	Blackwell Scientific Publications. Oxford,
VOLUME/ISSUE/PAGES:	1986 Mar;24(3):239-42 239-42
DATE:	1986
AUTHOR OF ARTICLE:	Kaufman FR; Costin G; Reid BS
TITLE OF ARTICLE:	Autonomous ovarian hyperfunction followed by gonad
ISSN:	0300-0664
OTHER NOS/LETTERS:	Library reports holding volume or year 0346653 3085997
SOURCE:	PubMed
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Clinical Endocrinology (1986), **24**, 239–242

AUTONOMOUS OVARIAN HYPERFUNCTION FOLLOWED BY GONADOTROPHIN-DEPENDENT PUBERTY IN McCUNE–ALBRIGHT SYNDROME

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(Received 17 June 1985; returned for revision 30 July 1985; finally revised 14 August 1985; accepted 30 September 1985)

SUMMARY

A 5-year-old girl with the McCune–Albright syndrome presented with precocious puberty secondary to autonomously functioning ovarian cysts, followed by true central puberty. Progression from gonadotrophin-independent to gonadotrophin-dependent precocious puberty may occur from elevated sex steroid levels leading to the early maturation of the hypothalamic-pituitary axis.

The aetiology and pathogenesis of the McCune–Albright syndrome (Albright *et al.*, 1937), which includes the triad of sexual precocity, polyostotic fibrous dysplasia and cutaneous pigmentation, remain unknown. It has been postulated that precocious puberty is mediated either through the central hypothalamic-pituitary axis (gonadotrophin-dependent true precocious puberty) or through the autonomous hyperfunction of the gonads (gonadotrophin-independent pseudopuberty) (Comite *et al.*, 1984; Foster *et al.*, 1984; Wierman *et al.*, 1985). We describe a 5-year-old girl with the McCune–Albright syndrome and pseudopuberty secondary to the periodic development of hormonally active ovarian cysts followed by the onset of gonadotrophin-dependent precocious puberty.

CASE REPORT

A 5-year-old girl presented with a 6-month history of breast development and one episode of vaginal bleeding. There was no history of exposure to exogenous oestrogens. On physical examination, her height was 108·4 cm (50th percentile) and weight was 19·8 kg (50th percentile), compatible with the family heights. She had Tanner Stage 3 breast development with hyperpigmented areolae, oestrogenization of the vaginal mucosa and

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palpable adnexal masses bilaterally. There was no axillary or pubic hair. Irregular hyperpigmentation of the right anterior thigh and buttock was present. The thyroid gland, neurological and ophthalmic examinations were normal. Skeletal radiographs showed multiple lucent defects with sclerotic margins consistent with polyostotic fibrous dysplasia. The bone age was 5 years. Basal and dynamic endocrine studies are detailed below.

Over the next 3 years without treatment, the patient had multiple episodes of vaginal bleeding at 5 4/12, 5 10/12, 6 4/12, 7 10/12, 8, 8 1/12 and 8 2/12 years of age. At 6 years of age her height (117·0 cm) had increased to the 75th percentile and remained so at 8 2/12 years. When she was 7 1/2 years old her bone age was 8 10/12 years, within 2 SD for chronological age and at 8 2/12 years the bone age advanced to 10 years. Cerebral computerized tomography was normal.

MATERIAL AND METHODS

The determination of serum gonadotrophins and oestradiol (E_2) levels were performed in the basal state, every 30 min through the night and after stimulation with luteinizing-hormone releasing hormone (LHRH) (Factrel). Factrel, 100 μg, was given by intravenous bolus infusion and FSH, LH and E_2 were measured every 15 min for 1 h and then hourly for 2 h. Serum hormone determinations were made by specific radioimmunoassays. LH and FSH results were expressed as milliinternational units per ml (WHO-68-40 was the reference standard for LH and WHO-69-104 for FSH). Pelvic ultrasound was done on Ausonics Octoson.

RESULTS

Results of basal hormone levels, LHRH stimulation tests and pelvic ultrasound evaluations are given in Table 1. During the first two years of observation, basal FSH and LH levels were in the prepubertal range and E_2 levels were elevated. Whilst on presentation and at 5 9/12 and 6 3/12 years of age there was no elevation of gonadotrophins after LHRH, at 7 1/2 years of age there was a six-fold increase in FSH and a 3 1/2 fold increase in LH after LHRH stimulation. At 8 and 8 2/12 years of age, there was a pubertal gonadotrophin response to LHRH and at 8 3/12 years peak nocturnal FSH, LH and E_2 levels were 2·5 mIU/ml, 7·1 mIU/ml, and 20 pg/ml, respectively.

Ultrasound examinations indicated periodic fluctuations in ovarian size and the appearance and disappearance of ovarian cysts (Fig. 1). Initially, elevation of serum E_2 was documented when cysts were present and episodes of vaginal bleeding followed regression of ovarian cysts and decrease in E_2 levels. After 8 years of age, ovarian cysts were still seen although excessive E_2 production could not be demonstrated.

DISCUSSION

This patient demonstrates the classic findings in McCune Albright syndrome of polyostotic fibrous dysplasia, cutaneous pigmentation, and precocious sexual development (Albright *et al.*, 1937). Although other endocrinopathies have been reported in McCune–Albright syndrome, none was evident in our patient. The high oestradiol levels

Table 1. Clinical, laboratory and radiological data

Age (years)	BA*	FSH (mIU/ml) Basal	FSH (mIU/ml) Stim‡	LH (mIU/ml) Basal	LH (mIU/ml) Stim‡	E_2 (pg/ml) Basal	E_2 (pg/ml) Stim‡	Ovarian size (mm)† Left	Ovarian size (mm)† Right
5 2/12	5	1·7	1·7	2·8	3·5	1285	1489	13·5 × 22·8	11·9 × 27·3§
5 3/12		1·6		1·8		31			
5 4/12		1·6		2·4		38		18·9 × 27·6	16·8 × 32·0§
5 6/12	6	1·6		3·7		20			
5 9/12		1·6	1·6	2·8	3·5	70	58	22·8 × 17·1	27·5 × 13·0§
5 11/12		1·6		4·6		21		12·2 × 8·0	8·7 × 12·7
6 1/12	8	4·3		4·3		20			
6 3/12		1·6	2·6	4·2	5·4	53	50	22·8 × 17·6	14·5 × 26·2§
6 6/12		1·2		2·0		30			
7 6/12	8 3/4	1·0	6·0	1·9	6·9	10	14	8·8 × 11·5	9·5 × 13·6
7 8/12		1·2		1·7		12		8·9 × 10·2	9·6 × 12·0
8 0/12	8 3/4	1·0	9·8	2·0	39·0	12	23	25·0 × 15·0	31·0 × 15·2§
8 2/12		1·5	5·6	1·7	16·0	32	46		
8 3/12	10	2·5		7·1		20		25·0 × 18·0	28·0 × 18·0§

* Bone age.

† Ovarian size from ultrasound measurements, normal less than 10·0 × 10·0 mm.

‡ Maximal response after 100 μg Factrel (normal prepubertal values, FSH < 15 mIU/ml, LH < 10 mIU/ml, E_2 < 20 pg/ml), (Grumbach *et al.*, 1974).

§ Indicates presence of bilateral ovarian cysts.

For oestradiol; 10 pg/ml = 36·76 pmol/l.

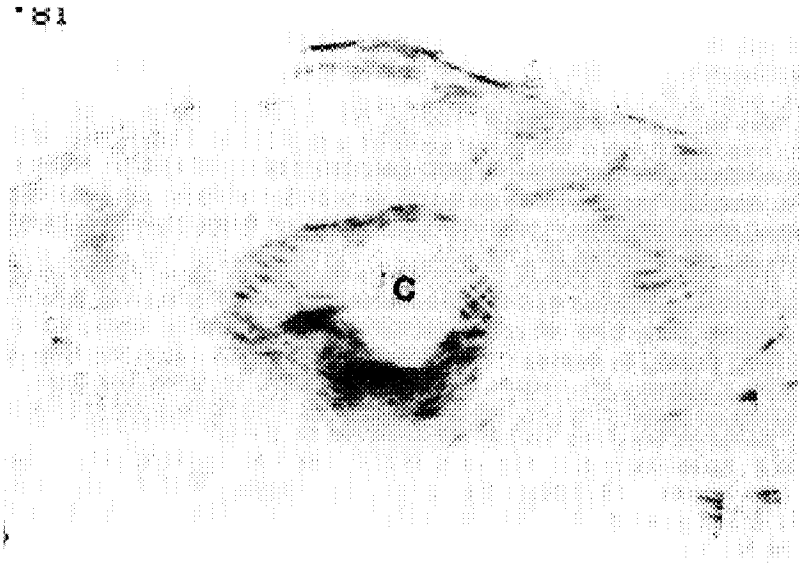

Fig. 1. Ultrasound image of left ovary demonstrating large cyst (C) at 5 9/12 years of age.

and prepubertal values for gonadotrophins in the basal and stimulated states, on presentation and during the first two years of follow-up, indicate that there was autonomous ovarian production of oestrogen without stimulation from the hypothalamic-pituitary axis. Oestrogen was apparently produced in ovarian cysts and there was an excellent correlation between the size of the ovary and oestradiol levels.

At 8 years of age, with a bone age of 8 10/12 years, the patient appeared to enter true central puberty and demonstrated a pubertal gonadotrophin response to LHRH stimulation. Our patient's course suggests that priming of the hypothalamic-pituitary axis occurred following prolonged exposure to gonadal steroids, a situation similar to that observed in patients with congenital adrenal hyperplasia in whom treatment is delayed (Pescovitz *et al.*, 1984). Since the onset of central puberty, our patient has had increased regularity of menses suggesting that the autonomous functioning of the ovary may have abated. Further follow up will be required to see whether the central secretion of gonadotrophins will permanently suppress excessive oestrogen secretion by autonomous ovarian cysts.

The origin of sexual precocity in McCune–Albright syndrome may be either central or secondary to autonomous ovarian hyperfunction (Comite *et al.*, 1984; Foster *et al.*, 1984; Wierman *et al.*, 1985). We believe our patient is the first to be reported with both, although it is likely that other patients have had similar progression. Patients reported with gonadotrophin-dependent puberty by others (Foster *et al.*, 1984) were older than 8 years of age when initially evaluated, the age at which central puberty developed in our patient. It is conceivable that these children, like our patient, progressed from gonadotrophin-independent to gonadotrophin-dependent puberty secondary to the early maturation of the hypothalamic-pituitary axis from exposure to elevated sex steroid levels. It is likely that the pseudopuberty associated with McCune–Albright syndrome initiates the onset of true complete puberty in these patients.

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